IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	MDL Docket No. 2738
This Document Relates To All Cases	)	

DEFENDANTS JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION TO EXCLUDE THE OPINIONS OF DEFENDANTS' EPIDEMIOLOGY EXPERTS

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Plaintiffs' arguments seeking to exclude the opinions of Drs. Karla Ballman, Gregory Diette and Christian Merlo (collectively, "defendants' epidemiology experts") oversimplify these experts' methodologies, misrepresent the science and scientific consensus on numerous issues, and impose standards that are not supported by the law. Plaintiffs also distort the Bradford Hill framework in a manner that seems more focused on resuscitating their own experts' flawed analyses than highlighting any genuine flaws in the methodologies of defendants' three epidemiology experts.

First, plaintiffs focus heavily on the "consistency" prong of Bradford Hill, arguing that defendants' epidemiology experts' methodologies for analyzing whether the talc studies demonstrate a consistency of association were unreliable. In so arguing, plaintiffs contend that defendants' experts employed a "mechanical two-step approach" to this issue that only considered whether the results of studies are statistically significant and the general principle that cohort studies provide more valuable evidence than case-control studies.

This argument grossly mischaracterizes defendants' epidemiology experts' opinions. As made clear in their reports, defendants' experts found that the body of epidemiological evidence did not show a consistent association in large part because the studies reported divergent magnitudes of risk, if any (regardless of statistical significance or hierarchies of evidence). Defendants' epidemiology

experts also criticize plaintiffs' experts' methodologies because plaintiffs' epidemiology experts attempted to explain away the inconsistency between cohort studies and case-control studies by attacking the cohort studies as unreliable. As defendants' epidemiology experts explain in their reports, these attacks are speculative and results-oriented and do not justify plaintiffs' experts' decision to ignore the negative results of the cohort studies.

A substantial portion of plaintiffs' brief focuses on rejecting two fundamental aspects of epidemiology: (1) the analytical practice of considering whether study results are statistically significant; and (2) the hierarchy of scientific evidence. Contrary to plaintiffs' arguments, the scientific community continues to consider and report statistical significance and to recognize that certain study designs are generally stronger than others. For this reason, federal courts, including the Third Circuit and this Court, have embraced, rather than rejected, these concepts. In short, considering statistical significance and the evidentiary hierarchy are key elements of a reliable causation methodology, not missteps that render defendants' epidemiology experts' opinions unreliable.

Second, plaintiffs fail to show that defendants' epidemiology experts "misstated and misapplied" the dose response and biological plausibility considerations of the Bradford Hill framework. Plaintiffs argue that evidence of dose response is "unnecessary" to demonstrate causation, but the circumstances in

which scientists may reliably minimize the importance of dose response – i.e., when there are little to no data on the issue – are unlike those here, where there are substantial data refuting the notion that the risk of ovarian cancer rises as talc use increases, as defendants' epidemiology experts explain. Indeed, as described by the authors of the Health Canada Draft Screening Assessment – a source that plaintiffs cite throughout their brief but is conspicuously absent from their dose-response arguments – "***none***" of the studies "***demonstrate both a clear dose-response trend and statistical significance***."[1] In short, plaintiffs have failed to show that defendants' experts evaluated the evidence on dose response unreliably.

Plaintiffs are similarly incorrect that defendants' epidemiology experts did not reliably consider biological plausibility. Plaintiffs argue that a biological mechanism theory must merely "'make sense' biologically," ignoring the decisions of numerous courts that have held that untested and unsupported hypotheses do not pass muster under *Daubert*. But plaintiffs' effort to use semantics to try to diminish the showing needed for this factor is in any event moot, since defendants' experts explained that plaintiffs' theory that externally-applied talc particles

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[1] Health Canada, Draft Screening Assessment: Talc ($Mg_3H_2(SiO_3)_4$), at 20-21 (Chem. Abstracts Serv. Registry No. 14807-96-6) (2018) ("Draft Screening Assessment") (attached as Ex. A58 to the Omnibus Certification of Julie L. Tersigni ("Tersigni Cert."), May 7, 2019 (ECF No. 9723-2)) (emphasis added).

migrate up the female genital tract and cause chronic inflammation leading to cancer does not make sense for a number of reasons, which are discussed below.

Third, plaintiffs' argument that Dr. Merlo's opinions should be excluded because he "[d]id [n]ot [p]erform a [c]omplete [c]ausation [a]nalysis" is meritless. As Dr. Merlo explained, since the talc literature demonstrates a weak association, inconsistency among studies and no dose response, it was unnecessary for him to consider other Bradford Hill factors. Without a single one of these three factors satisfied, the epidemiology essentially refutes a causal link, and biological plausibility alone could not demonstrate causation.

Finally, plaintiffs' argument that defendants' epidemiology experts unreliably cherry-picked statements by plaintiffs' experts in criticizing their opinions regarding the strength of association factor only shows that plaintiffs' experts' evaluation of this factor was indefensible. Plaintiffs cannot escape the fact that their experts have characterized the association as "extremely strong," "significant," "strong" and "compelling," and "high and significant," by claiming that those quotes were cherry-picked. Nor is there any merit to their argument that the strength factor is a "qualitative" measure rather than a "quantitative" one. Notably, plaintiffs' attempt to distance themselves from words used by their own experts serves only to underscore that not even plaintiffs believe that the talc epidemiology demonstrates a "strong" association.

Plaintiffs' effective abandonment of the "strength," "dose response" and "biological plausibility" factors leaves them standing before this Court and arguing that only one Bradford Hill criterion matters – consistency – and that consistency can be manufactured by ignoring an entire category of studies and abandoning statistical significance. This untenable, litigation-driven position highlights the unreliable nature of plaintiffs' theories and their own experts' opinions rather than supporting plaintiffs' attacks on the methodologies of the defense experts.

For all of these reasons, discussed further below, the Court should deny plaintiffs' motion.

BACKGROUND

A. Karla Ballman, Ph.D.

Dr. Ballman is the "Chief of the Division of Biostatistics and Epidemiology at Weill Cornell Medicine."[2] Dr. Ballman previously served as the Chair of the Mayo Clinic (Rochester, Minnesota) Division of Biostatisticians, where she was involved in hundreds of clinical studies, including both clinical trials and observational studies.[3] She holds both a Master's degree and a Ph.D. from the Massachusetts Institute of Technology in Operations Research, which includes

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[2] (*See* Expert Report of Karla Ballman, Ph.D. ("Ballman Rep.") at 1, Feb. 25, 2019 (attached as Ex. C25 to Tersigni Cert.).)

[3] (*Id.*)

substantial training in epidemiology.[4] Her career has focused on ensuring that study designs are "scientifically rigorous, that the data are appropriate and of high quality, and that interpretations made are supported by the data."[5] She is a co-author of more than 200 manuscripts, most of which relate to research on a variety of cancers.[6] She additionally serves as the Deputy Editor of the *Journal of Clinical Oncology* (one of the top cancer journals in the world), where she evaluates manuscripts assessing risk factors for cancer; has worked on scientific review panels assessing studies' scientific rigor and impact on cancer outcomes; and has served on more than 65 grant review panels, including for grants from the National Cancer Institute, the National Institutes of Health and the Department of Defense Congressionally Directed Medical Research Programs.[7] Dr. Ballman has also earned a number of accolades throughout her career, including the Macalester College Distinguished Alumni in Science award in 2015 and the Mayo Clinic's Health Sciences Research Distinguished Teaching Award in 2004.[8]

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4 (*Id.*)

5 (*Id.*)

6 (*Id.*)

7 (*Id.* at 1-2.)

8 (*See id.*, Ex. A at 14 (Weill Cornell Medical College *Curriculum Vitae* of Karla V. Ballman).)

B. Gregory Diette, M.D., M.H.S.

Dr. Diette is an attending physician and professor of medicine at Johns Hopkins University with appointments in the Departments of Epidemiology and Environmental Health Sciences in the Johns Hopkins Bloomberg School of Public Health.[9] He received his M.D. from the Temple University School of Medicine, completed his residency at the Hospital of the University of Pennsylvania and performed a fellowship in pulmonary and critical care medicine at Johns Hopkins.[10] In addition to his comprehensive medical training, he received an M.H.S. in Epidemiology and Clinical Epidemiology from the Johns Hopkins Bloomberg School of Public Health.[11] Dr. Diette's "areas of clinical expertise include internal medicine, pulmonary medicine and critical care medicine," and his "areas of research include environmental impacts on lung disease and epidemiology of chronic diseases."[12] Dr. Diette has published more than 200 peer-reviewed studies.[13] He is also a peer reviewer for multiple journals; has repeatedly taught advanced research methods in epidemiology; and has participated in the

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9 (Expert Report of Gregory Diette, M.D., M.H.S. ("Diette Rep.") at 2, Feb. 25, 2019 (attached as Ex. C18 to Tersigni Cert.).)

10 (*Id.*)

11 (*Id.*)

12 (*Id.*)

13 (*Id.*)

"Methods in Epidemiologic, Clinical and Operations Research program" with the American Thoracic Society.[14]

C. Christian Merlo, M.D., M.P.H.

Dr. Merlo is an "expert in the methodologic approach to the study of disease."[15] He is currently an associate professor of epidemiology at Johns Hopkins University.[16] He is also an attending physician and is board certified in internal medicine, pulmonary medicine and critical care medicine.[17] Dr. Merlo received his medical degree from the Georgetown University School of Medicine, completed his residency in internal medicine at the Georgetown University Medical Center (where he served as Chief Resident) and completed a fellowship in Pulmonary and Critical Care Medicine at Johns Hopkins Hospital.[18] He also earned a master's degree in public health ("MPH") from the Johns Hopkins Bloomberg School of Public Health.[19] Dr. Merlo's years of research have focused

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14 (*Id.*)

15 (Expert Report of Christian Merlo, M.D., M.P.H. ("Merlo Rep.") at 2, Feb. 25, 2019 (attached as Ex. C13 to Tersigni Cert.).)

16 (*Id.* at 1.)

17 (*Id.*)

18 (*Id.*; *see also* Dep. of Christian Merlo, M.D., M.P.H. ("Merlo Dep.") 17:22-18:4, Apr. 18, 2019 (attached as Ex. B9 to Tersigni Cert.) ("I have lots of expertise. I have expertise in internal medicine and a broad range of pulmonary medicine, a broad range of critical care medicine as well as lung transplantation.").)

19 (Merlo Rep. at 1.)

on the design of clinical studies investigating the impact of environmental and infectious exposures, and he has taught courses for more than 15 years on study design and analysis.[20] In addition, Dr. Merlo is a clinical investigator with special training in clinical epidemiological trial design, conduct and analysis.[21] He has authored or co-authored more than 70 manuscripts, book chapters and commentaries on topics involving cystic fibrosis and lung transplantation and beyond, and is a current investigator on National Institutes of Health- and industry-funded clinical trials.[22] Dr. Merlo has also earned a host of awards and honors, including the Johns Hopkins Fellows Teaching Award in 2010 and the NIH Loan Repayment Program Award for Clinical Research in 2005.[23]

ARGUMENT

The standard for the admission of expert testimony under Rule 702 and *Daubert* is fully set forth in defendants' Motion to Exclude Plaintiffs' Experts' General Causation Opinions ("General Causation Brief")[24] and further elaborated in their Response to Plaintiffs' Omnibus Brief Regarding the *Daubert* Legal

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20 (*Id.*)

21 (*Id.*)

22 (*Id.*)

23 (*Id.*, App. A at 12 (Curriculum Vitae of Christian A. Merlo, M.D., M.P.H.).)

24 (Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts' General Causation Ops. ("General Causation Br.") at 28-30, May 7, 2019 (ECF No. 9736).)

Standard ("Omnibus *Daubert* Opposition Brief").[25] In short, expert testimony is admissible when the witness is qualified and the opinion is "based on sufficient facts or data" and is "the product of reliable principles and methods" that have been "reliably applied . . . to the facts of the case." Fed. R. Evid. 702.

Drs. Ballman, Diette and Merlo each offer an opinion on whether perineal talc use has been shown to cause ovarian cancer and also address plaintiffs' experts' opinions on the same topic. Defendants' experts analyze these issues under the Bradford Hill framework,[26] which, as elaborated in defendants' General Causation Brief, entails at least nine relevant considerations: strength of association, consistency of association, specificity, temporality, coherence, dose response (or biological gradient), biological plausibility, experimental evidence and analogy.[27]

In seeking to exclude these experts, plaintiffs argue that: (1) all three applied a "discredited methodology for assessing 'consistency of association'"; (2) all three "appl[ied] the wrong standard for the 'dose response' and 'biologic

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[25] (*See generally* Defs.' Mem. of Law in Resp. to Pls.' Steering Committee's Omnibus Br. Regarding *Daubert* Legal Standard & Scientific Principles for Assessing General Causation (filed herewith and incorporated herein).)

[26] (*See* Ballman Rep. at 15-20; Diette Rep. at 4; Merlo Rep. at 30.)

[27] (General Causation Br. at 27 (citing Hill, *The Environment and Disease: Association or Causation?*, 58(5) Proc. Royal Soc'y Med. 295, 295-99 (1965) ("Hill 1965") (attached as Ex. A63 to Tersigni Cert.)).) The consideration of alternative causes is also considered by some to be an appropriate part of a Bradford Hill analysis. (*Id.* at 78 & n.182.)

plausibility'" Bradford Hill factors; (3) Dr. Merlo "fail[ed] to perform a complete causation analysis"; and (4) all three experts "'cherry-picked' sound bites from [plaintiffs' experts'] reports and depositions" in criticizing their opinions on strength of association.[28] In addition, plaintiffs mildly criticize defendants' experts' qualifications.[29] All of these arguments should be rejected.

I. DEFENDANTS' EPIDEMIOLOGY EXPERTS APPROPRIATELY ANALYZED CONSISTENCY OF ASSOCIATION.

Plaintiffs argue that defendants' experts evaluated consistency of association "using a flawed two-step methodology," which, according to plaintiffs, entailed "mechanical[ly]" (1) "[a]pplying statistical significance as the benchmark of consistency" and (2) following a hierarchy of evidence under which cohort studies and hospital-based case-control studies "automatically" outrank population-based case-control studies.[30] According to plaintiffs, the scientific community rejects the consideration of whether study results are statistically significant,[31] and it is a

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28 (Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude the Ops. of Defs.' Epidemiology Experts Karl Ballman, PH.D., Christian Merlo, M.D., MPH, Gregory Diette, M.D., MHS, and Jonathan Borak, M.D., DABT ("Pls.' Br.") at 57, 71-73, May 7, 2019 (ECF No. 9737-1).)

29 (*See id.* at 4-6.)

30 (*Id.* at 12-17, 38-41.)

31 (*Id.* at 20-28.)

"misconception" that there is a hierarchy of scientific evidence.[32] Rather, plaintiffs argue, their own experts "performed individual assessments of the strengths, weaknesses, and biases of the talc studies," whereas defendants' experts looked "solely [at] generic study design category."[33] As set forth below, these arguments are precisely backwards.[34]

A. Defendants' Experts Did Not Employ A Supposed "Mechanical Two-Step Process" For Analyzing Consistency Of Association.

As an initial matter, plaintiffs incorrectly characterize defendants' experts' methodologies as "mechanical[ly]" requiring that results be statistically significant and applying an improper evidentiary hierarchy. While defendants' experts did consider whether results were statistically significant and the relative value of different types of studies, they did not focus on these issues exclusively or address

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32 (*Id.* at 34-37.)

33 (*Id.* at 44-47.)

34 Plaintiffs argue that it is "'disingenuous'" for defendants' experts to argue that the talc studies have not shown a consistency of association, referring to a 2016 editorial by S.A. Narod as support for this proposition. (*Id.* at 12 (citing Narod, *Talc and Ovarian Cancer*, 141(3) Gynecol. Oncol. 410 (2016) ("Narod 2016") (attached as Ex. A97 to Tersigni Cert.)).) But plaintiffs misquote Narod. Narod did not state that it is disingenuous to deny a ***consistency*** of association; rather, he said that it would be disingenuous "'to state that there is ***no evidence*** that talc is associated with ovarian cancer.'" (*Id.* (emphasis added).) Defendants' experts do not contend that there is no evidence at all of an association. Rather, they have offered the opinions that there is weak, inconsistent evidence of an association in a subset of the observational studies.

them in a "mechanical" fashion. Plaintiffs' effort to isolate and caricature defendants' experts' opinions on these points leads them to ignore a number of additional factors that the experts considered in assessing whether there is a consistency of association among the relevant epidemiological studies.[35]

Dr. Ballman. Dr. Ballman's discussion of consistency of association covers numerous issues other than lack of statistical significance and the evidentiary

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[35] Plaintiffs propose that a reliable analysis of consistency "should consider whether the confidence intervals overlap among the various study designs." (Pls.' Br. at 46.) But this would be an undiscerning method of judging consistency, since confidence intervals can be exceedingly wide and varied, and accordingly may easily overlap. Two talc studies from 2016 with barely overlapping confidence intervals illustrate this. *Compare* Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*, 27(6) Epidemiol. 797, 797 (abstract) (2016) (attached as Ex. A47 to Tersigni Cert.) (cohort study reporting OR 0.73 (95% CI = 0.44-1.2)) *with* Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*, 27(3) Epidemiology 334, 334 (abstract) (2016) ("Cramer 2016") (attached as Ex. A25 to Tersigni Cert.) (case-control study reporting RR 1.33 (95% CI = 1.16-1.52)). Not even plaintiffs' experts seriously contend that these studies are consistent; rather, their approach is to criticize and downplay the Gonzalez study. (*See* Expert Report of Rebecca Smith-Bindman, M.D. ("Smith-Bindman Rep.") at 21, Nov. 15, 2018 (attached as Ex. C36 to Tersigni Cert.); Expert Report of Sarah E. Kane ("Kane Rep.") at 26, Nov. 15, 2018 (attached as Ex. C38 to Tersigni Cert.); Expert Report of Ellen Blair Smith ("Smith Rep.") at 15, Nov. 15, 2018 (attached as Ex. C16 to Tersigni Cert.); Expert Report of Jack Siemiatycki, M.Sc., Ph.D. ("Siemiatycki Rep.") at 57, Nov. 16, 2018 (attached as Ex. C21 to Tersigni Cert.); Expert Report of Sonal Singh, M.D., M.P.H. ("Singh Rep.") at 46-47, 51-53, Nov. 16, 2018 (attached as Ex. C40 to Tersigni Cert); Expert Report of Patricia G. Moorman, M.S.P.H., Ph.D. ("Moorman Rep.") at 29, Nov. 16, 2018 (attached as Ex. C35 to Tersigni Cert.).)

hierarchy.[36] Indeed, far from resting solely on a consideration of those issues, Dr. Ballman explains that "it is not necessary [for consistency] that all studies have statistically significant results" because statistical significance can be a function of sample size.[37] Instead, Dr. Ballman focuses on the fact that the "magnitude of association" – without regard for statistical significance – has varied enormously across the talc studies, with cohort and case-control studies having "meaningfully different" "magnitude[s] of the associations" and "the largest reported association [in case-control studies being] almost 4 times greater than the smallest reported association"[38] She also explains in detail that "the wide range of associations within the case-control studies" can be attributable to the use of different control populations, which is problematic because "if there truly were a causal relationship, it would be expected to be seen in different control groups."[39] She further observes

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36 (Ballman Rep. at 24-29.)

37 (*Id.* at 17.)

38 (*Id.* at 24-26 (explaining that case-control studies ranged from 0.92 to 3.90 and cohort studies ranged from 0.73 to 1.12 and that, as to the case-control studies, "[a] range of the smallest association to the largest being four times different is not an indication of stability of the magnitude of association").)

39 (*Id.* at 25.)

that hospital-based and population-based case-control studies had divergent ranges of association magnitudes.[40]

Dr. Ballman's discussion of statistical significance is also much more nuanced than plaintiffs' portrayal. Dr. Ballman explains that the "divergence [between cohort and case-control studies] is all the more striking" because it is clear that the cohort studies' failure to detect a statistically significant association ***is not*** a function of the size of those studies (contrary to plaintiffs' experts' contentions that the cohort studies did not follow enough women).[41] She also demonstrates that the cohort studies contained "approximately 1,400 women diagnosed with ovarian cancer and more than 200,000 women who were not," giving them "sufficient power" (meaning they followed enough women) to detect a statistically significant "association of 1.26, [which is what was] observed in the case-control studies."[42]

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[40] (*Id.* at 25-26 ("The range of values for case-control studies with hospital controls was 1.13 to 1.70, and none of the results was statistically significant. This range is considerably smaller than what is seen in studies with population-based controls.").)

[41] (*Id.* at 26.)

[42] (*Id.*) Dr. Ballman's analysis is consistent with a textbook plaintiffs repeatedly cite, which explains that whether results are statistically significant depends on "differences in sample size or the strength of association." *See* Oleckno, *Epidemiology: Concepts and Methods* (1st ed. 2008) ("Oleckno 2008") at 221-22 (attached as Ex. 65 to Pls.' Br.) (further explaining that "[i]n isolation one

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In addition, rather than relying on a general evidentiary hierarchy, Dr. Ballman deems the inconsistency between case-control and cohort studies highly important only after considering plaintiffs' experts' rejection of cohort study results.[43] For example, in addition to arguing that the cohort studies did not follow enough women to detect risk, plaintiffs' experts also contend that the cohort studies did not follow women for a long enough period in light of the alleged latency period of ovarian cancer and did not ask sufficient questions regarding the extent of perineal talc exposure – criticisms that Dr. Ballman demonstrates are speculative and blown out of proportion.[44] And contrary to plaintiffs' claim that defendants' experts ignored this issue, Dr. Ballman refutes the theory that the talc studies are consistent because they generally reported odds ratios above 1.0,[45] explaining that if this were a metric for measuring consistency, it would deem "results that cover a range of 100-fold from smallest observed value to largest

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cannot be sure if a p-value is more a reflection of sample size or strength of the association or both") (cited in Pls.' Br. at 27, 49, 50, 58).

[43] (Ballman Rep. at 26, 28.)

[44] (*Id.* at 26, 28 (explaining that "the amount of extensive questioning . . . does not matter" since "[i]t is relatively easy to measure if someone ever used something," and that the latency period "is not a valid concern" since "women who used talcum powder had been using it 10-20 or more years" when asked about talc usage).)

[45] (Pls.' Br. at 18 (arguing that defendants' experts "ignored the overall positive association shown by the talcum powder data in virtually every study").)

observed value" as consistent – rendering the approach overly "broad."[46] Dr. Ballman also explains that the fact that different study designs (cohort versus case-control) tended to produce different results is significant – not solely, as plaintiffs contend, on the basis of an evidentiary hierarchy, but specifically in light of Hill's own statement that he would place "a good deal of weight upon similar results reached in quite different ways, e.g., ***prospectively and retrospectively***,'" in evaluating the consistency factor.[47]

Finally, Dr. Ballman rejects the argument that the meta-analyses demonstrate consistency – an argument pressed in plaintiffs' brief[48] – explaining that "the consistency of the estimates across meta-analyses is uninformative" because "these studies analyze overlapping sets of studies."[49]

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[46] (Ballman Rep. at 26-27.) Dr. Ballman similarly points out that Dr. Siemiatycki is wrong to argue that a non-causal association would produce an equal number of results above and below 1.0, since that "would only be true if there were no residual confounding or biases within studies, which is not true for observational studies." (*Id.* at 27.) She explains that "if there were clinical trial data, it then would be expected that roughly half the studies would have a risk ratio less than one and half greater than one if the relationship were not causal. However, it is likely that the case-control studies have recall biases as well as other residual confounding, which would mean that they are consistently estimating a biased association." (*Id.*)

[47] (*Id.* at 28 (emphasis added) (quoting Hill 1965).)

[48] (Pls.' Br. at 11.)

[49] (*Id.* at 25, 27.)

***Dr. Diette*.** Dr. Diette observes in his discussion of consistency that "the prospective epidemiologic studies (cohort studies) do not show a statistically significant association between perineal talc use and ovarian cancer, while only a subset of the population-based case-control studies does" and that "[t]he fact that none of the cohort studies found a statistically significant association between talc use and ovarian cancer is critical in this regard."[50] However, statistical significance was far from the only factor Dr. Diette considered.

Dr. Diette's discussion of consistency follows his discussion of strength of association, in which he explores the results of different talc studies in detail and explains why plaintiffs' experts' arguments criticizing the cohort studies (which are essential for their purported finding of consistency) are incorrect.[51] This discussion explicitly informs his analysis of consistency of association,[52] where he additionally explains, like Dr. Ballman, that "case-control studies and cohort

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50 (Diette Rep. at 24 (citation omitted).)

51 (*Id.* at 8-15, 19-21.)

52 (*Id.* at 24 ("As set forth above [in strength of association discussion], the prospective epidemiologic studies (cohort studies) do not show a statistically significant association, while only a subset of the population-based case-control studies does.").)

studies found varying strengths of association that do not amount to consistent results."[53]

Also like Dr. Ballman, Dr. Diette's discussion of consistency considers and rejects plaintiffs' experts' arguments criticizing the cohort studies.[54] In particular, he explains that these criticisms "assume[] that the results of some studies are not consistent, or else there would be no reason for [plaintiffs' experts] to find fault with the cohort study designs in order to explain why their results do not negate the findings from other studies."[55] He also explains that plaintiffs' experts' argument that there is consistency because most studies reported odds ratios above 1.0 ignores the high variation in effect magnitude among studies, and that in any event, this approach to assessing consistency "is so broad that it is nonsensical, as it would consider near-null associations and definitively causal associations consistent."[56] He further explains that plaintiffs' experts' arguments regarding the cohort studies' sample size and statistical power ignore the peer-reviewed Berge

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53 (*Id.* at 26.)

54 Dr. Diette primarily addresses these arguments in his earlier discussion of strength of association, and expressly incorporates this discussion into his treatment of the issue of consistency. (*Id.* at 25 (explaining that plaintiffs' expert Dr. Anne McTiernan's "criticisms of cohort studies are misplaced, as previously discussed").)

55 (*Id.* at 25.)

56 (*Id.* at 26.) Here, again, defendants' experts did not "*ignore*[] the overall positive association shown" in most talc studies. (*See* Pls.' Br. at 18.)

study's demonstration that these studies had adequate power and are "speculative because there is no way to know whether a larger sample would provide the same or a different estimate or whether that estimate would be statistically significant."[57]

Finally, Dr. Diette addresses "[o]ther inconsistencies . . . in the literature," including that studies looking at talc use on condoms and diaphragms have not found an association with ovarian cancer.[58] And like defendants' other experts, he rejects plaintiffs' argument that meta-analyses are evidence of consistency, explaining that because these studies "analyze overlapping sets of individual studies, it is not surprising that meta-analyses yield consistent results."[59]

Dr. Merlo. Dr. Merlo placed significant weight on the fact that cohort studies and population-based case-control studies did not report statistically significant associations, while only a subset of the population-based case-control studies did.[60] Given that scientists continue to widely employ significance testing

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[57] (Diette Rep. at 26 (citing Berge et al., *Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis*, 27(3) Eur J Cancer Prev. 248 (2018) ("Berge 2018") (attached as Ex. A11 to Tersigni Cert.)), which "demonstrat[ed] that the cohort studies collectively had sufficient power to detect a 1.25 relative risk if one existed" and concluded that "'low power of cohort studies cannot be invoked as an explanation of the heterogeneity of results'").)

[58] (*Id.* at 24-25.)

[59] (*Id.* at 25-26.)

[60] As Dr. Merlo explains, "[c]onsistency in relative risks that are not statistically significant . . . does not provide any degree of confidence that the

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and recognize that it is a valuable tool for discerning the potential effect of chance, as explained below and in defendants' Omnibus *Daubert* Opposition Brief, it is preposterous to call this "unreliable." In any event, the lack of statistical significance was not the only factor Dr. Merlo considered.

Indeed, Dr. Merlo's statements on this issue were made in the context of his entire report, which among other things, includes a 14-page discussion of each individual epidemiological study – i.e., precisely the sort of analysis plaintiffs argue was required.[61] He reiterates his summary of these studies' strengths and weaknesses when he later discusses consistency, explaining that "each one of these observational studies has limitations (recall bias and confounding in case-control studies; lack of repeated measure of exposure in cohort studies)" – and that "the studies that were used in all of the meta-analyses were of limited quality."[62]

Finally, plaintiffs also argue that a table Dr. Merlo assembled summarizing all of the individual talc studies' results "clearly represents the two-step approach"

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claim of association made by the study is more than random chance." (Merlo Rep. at 31, 44-45.)

[61] (*Id.* at 13-26; *contra* Pls.' Br. at 44-47 (explaining that an evaluation of consistency requires "perform[ing] individual assessments of the strengths, weaknesses, and biases of the talc studies").)

[62] (Merlo Rep. at 31.)

because it is "sorted by significance and design."[63] But Dr. Merlo's inclusion of this table (which is "sorted" by design and date, not significance) does not mean that significance and the evidentiary hierarchy were the only things he considered, as his broader discussion of each study makes plain.[64]

In sum, defendants' experts did not follow a "mechanical two-step process" in judging whether the talc studies show a consistency of association. In addition to observing a lack of statistical significance in most studies and that cohort studies and case-control studies diverged (both in terms of significance and magnitude), defendants' epidemiology experts observed substantial variations in the magnitude of association reported in different studies, specifically considered and rejected plaintiffs' experts' theories for why talc cohort studies might be less accurate and explained that meta-analyses do not provide meaningful evidence of consistency.

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63 (Pls.' Br. at 38-40 (citing Merlo Rep. at 38-39).)

64 Plaintiffs additionally argue that the authors of a 1992 hospital-based case-control study disagreed with Dr. Merlo as to whether their non-significant results were consistent with other studies' positive and significant results. (Pls.' Br. at 41-43 (discussing Rosenblatt 1992).) But what the authors of one study stated in 1992 says little about what a reliable consistency analysis would conclude based on the totality of the evidence today. For example, the Rosenblatt authors could not compare their results to a hospital-based study published the next year (Tzonou 1993) that reported a non-significant odds ratio of 1.05 and a confidence interval highly similar to that reported in Rosenblatt. (*See* Pls.' Br. at 39 (showing these results in Dr. Merlo's chart).) Nor could the Rosenblatt authors compare their results to those of the four cohort studies published since 2000 that have also found non-significant results below or barely above 1.0.

Plaintiffs' mischaracterization of defendants' experts' methodologies for assessing consistency of association should therefore be rejected.

B. Defendants' Experts Appropriately Considered The Import Of Statistical Significance And The Hierarchy Of Evidence.

In any event, plaintiffs are wrong that the concept of statistical significance and the notion that there is a well-established hierarchy of scientific evidence have lost mainstream acceptance. To the contrary, and as discussed in defendants' Omnibus *Daubert* Opposition Brief, consideration of these issues is part of what made defendants' experts' methodologies reliable, and as fully set forth in defendants' General Causation Brief, ***plaintiffs and their experts*** are the ones who have taken unreliable outlier positions in suggesting that statistical significance and the evidentiary hierarchy simply do not matter.[65]

1. Considering Statistical Significance Is Generally Accepted And Not "Universally Condemned" As Plaintiffs Argue.

Plaintiffs take the position in their briefing, as they did in depositions of defendants' experts, that the practice of considering whether study results are statistically significant "has been universally *condemned* in both the epidemiologic

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[65] (General Causation Br. at 9-12 & n.20, 61-66.)

and statistical communities, *including by Professor Hill himself*."[66] This claim could not be further off-base.

First, the notion that science has abandoned the longstanding practice of considering whether study results are statistically significant is demonstrably false. That practice is alive and well. The most prominent scientific publications in the world – such as the *New England Journal of Medicine*, the *Journal of the American Medical Association* and *Emerging Infectious Diseases* – continue to publish articles that discuss whether results are statistically significant.[67] And

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66 (Pls.' Br. at 18.)

67 *See, e.g.*, King et al., *A Trial of a Triple-Drug Treatment for Lymphatic Filariasis*, 379 New Engl. J. of Med. 1801, 1804-05, 1807 tbl. 2 (2018) (attached as Ex. A167 to Suppl. Certification of Julie L. Tersigni ("Suppl. Tersigni Cert.")) (conducting detailed analysis of statistical significance and concluding that the tested three-drug regimen was superior to a two-drug regimen where the former "resulted in significantly greater microfilarial clearance" at a level of "$P = 0.02$"); Wise et al., *Effect of Aclidinium Bromide on Major Cardiovascular Events and Exacerbations in High-Risk Patients With Chronic Obstructive Pulmonary Disease: The ASCENT-COPD Randomized Clinical Trial*, 321 JAMA 1693, 1693 (2019) (attached as Ex. A174 to Suppl. Tersigni Cert.) (finding that patients dosed with aclidinium saw a statistically significant reduced rate of pulmonary disease exacerbations, at the level of "$P < .001$" for "moderate to severe exacerbation[s]" and "$P = .006$" for "exacerbations requiring hospitalization"); Choi et al., *Risk Factors for* Elizabethkingia *Acquisition and Clinical Characteristics of Patients, South Korea*, 25 Emerging Infectious Diseases 42, 47-50 (2019) (attached as Ex. A162 to Suppl. Tersigni Cert.) (finding that use of mechanical ventilation among hospital patients was a risk factor for contracting *Elizabethkingia* infection, based on a statistically significant association at a level of "$P < 0.001$").

plaintiffs' own experts have similarly discussed statistical significance or lack thereof in their own peer-reviewed publications.[68]

Further, as discussed in more detail in defendants' Omnibus *Daubert* Opposition Brief, the Third Circuit has held that experts are not free to ignore whether study results are statistically significant, *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 793-94, 799 (3d Cir. 2017)

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[68] *See, e.g.*, Demb et al., *Optimizing Radiation Doses for Computed Tomography Across Institutions*, 177(6) JAMA Internal Med. 810, 814 tbl. 2 (2017) (attached as Ex. A163 to Suppl. Tersigni Cert.) (article co-authored by plaintiffs' expert Dr. Rebecca Smith-Bindman concluding that educational meetings were effective in lowering radiation doses where "*P* values represent[ing] test for change in means" before and after intervention were highly statistically significant at "<.001"); Mason et al., *Vitamin D_3 Supplementation During Weight Loss: A Double-Blind Randomized Controlled Trial*, 99 Am. J. Clin. Nutr. 1015, 1015 (2014) (attached as Ex. A169 to Suppl. Tersigni Cert.) (article co-authored by plaintiffs' expert Dr. Anne McTiernan concluding that Vitamin D_3 supplementation did not increase weight loss because of a lack of statistically significant results in relevant measurements – "all $P > 0.05$"); Moorman et al., *A Prospective Study of Weight Gain After Premenopausal Hysterectomy*, 18 J. of Women's Health 699, 702 (2009) (attached as Ex. A170 to Suppl. Tersigni Cert.) (finding an association between hysterectomies and weight gain where a statistical "model fully adjusted for all potential confounders . . . showed a difference in weight gain of 0.89 kg (~2.0 pounds, [*P*] = 0.04)" between test and control groups); Tisminetzky et al., *Magnitude and Impact of Multiple Chronic Conditions with Advancing Age in Older Adults Hospitalized with Acute Myocardial Infarction*, 272 Int'l J. of Cardiology 341, 342–44, 343 tbl. 2 (2018) (attached as Ex. A172 to Suppl. Tersigni Cert.) (article co-authored by plaintiffs' expert Sonal Singh finding relationships between treatment decisions and patient age, with differences in surgical decisions and certain medication decisions "[s]ignificant at $[P] \leq 0.001$").

("*Zoloft III*"), a decision plaintiffs relegate to a footnote in their brief.[69] *See also Bracco Diagnostics, Inc. v. Amersham Health, Inc.*, 627 F. Supp. 2d 384, 452 (D.N.J. 2009) (Wolfson, J.) (this Court holding that the opinions of an expert who "testified that the 0.05 p-value test for statistical significance was not grounded in solid science" were inadmissible; the expert's statements "regarding the use of the p-value [were] not properly based upon science and [were] not reliable"); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 892 F.3d 624, 642 (4th Cir. 2018) (affirming exclusion of Dr. Sonal Singh – also an expert for plaintiffs here – "because the plaintiffs 'failed to demonstrate that Dr. Singh's reliance on non-statistically significant "trends" is accepted in his field, that non-statistically significant findings have served as the basis for any

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[69] (Pls.' Br. at 28 n.65.) Plaintiffs correctly point out that the *Zoloft III* court did not "'state a bright line rule'" regarding statistical significance. (*Id.* (quoting *Zoloft III*).) However, they ignore the numerous statements the court made about the value of testing for statistical significance, set forth in the text above. They also incorrectly attempt to distinguish *Zoloft* by arguing that there were no studies reporting statistically significant results there. (*See id.*) But that is not true – the expert in *Zoloft* "presented five studies reporting a significant association between Zoloft and septal defects" but also was confronted with other results that were either positive and non-significant or negative and non-significant. 858 F.3d at 790-91. It was his treatment of the latter type of studies that the court deemed problematic, explaining that he improperly "emphasized the insignificance of results reporting odds ratios below 1 but not the insignificance of those reporting odds ratios above 1." *Id.* at 797. Plaintiffs do not accuse defendants' experts of making the same error here.

epidemiologist's causation opinion in peer-reviewed literature, or that standards exist for controlling the technique's operation'") (citation omitted).

Second, although some scientists have recently criticized the practice of placing dispositive weight on statistical significance,[70] these criticisms do not mean that it was unreliable for defendants' experts to consider statistical significance in their overall assessment of consistency of association or that plaintiffs' experts' contrary approach of ignoring statistical significance altogether was appropriate or reliable.

As an initial matter, many of the sources plaintiffs cite make it clear that they seek to challenge "pervasive" or "widespread" practices with respect to the consideration of statistical significance.[71] This is an implicit admission that the practices being questioned ***are*** generally accepted in the scientific community.

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[70] (*See generally* Pls.' Br. at 21-28.)

[71] *See* Amrhein et al., *Retire statistical significance*, 567 Nature 305, 305-06 (Mar. 21, 2019) ("Amrhein 2019") (attached as Ex. A8 to Tersigni Cert.); *see also, e.g.*, Rothman, *Six Persistent Research Misconceptions*, 29 J. Gen. Internal Med. 1060, 1064 (2014) ("Rothman 2014") (attached as Ex. 1 to Pls.' Br.) (describing the use of statistical significance as taking the "road" that is "crowded with others" and ending the article with "hope that calling attention to these misconceptions ***will spark the needed debates and be a catalyst for change***") (emphasis added); Wasserstein et al., *Moving to a World Beyond "p<.05"*, 73(Supp. 1) The American Statistician 1, 1 (2019) ("Wasserstein 2019") (attached as Ex. 61 to Pls.' Br.) (describing how articles presented in the publication "propose many new ideas" on statistical significance, which is evidence of "a world learning to venture beyond '$p < 0.05$.'").

Moreover, the articles plaintiffs cite generally criticize methodologies defendants' experts did not employ, i.e., considering non-statistically-significant positive results as equivalent to null results, and considering a lack of statistical significance as definitive evidence of a lack of consistency. For example, plaintiffs heavily rely on a recent "[C]omment" published in *Nature* seeking to "[r]etire statistical significance."[72] In that editorial, the authors (one of whom is an expert for plaintiffs in this litigation)[73] argued that scientists should not let a lack of statistical significance dictate "'that there is "no difference" or "no association,"'" or that "'two studies conflict because one has a statistically significant result and another did not.'"[74] But plaintiffs ignore that the *Nature* comment expressly did

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72 (Pls.' Br. at 22 (citing Amrhein 2019).)

73 That author – Dr. Sander Greenland – was disclosed as a consulting expert in plaintiffs' initial disclosures. (Pls.' Steering Committee's Initial Designation & Disclosure of Non-Case Specific Expert Witnesses at 6 (attached as Ex. I3 to Tersigni Cert.).) Plaintiffs repeatedly exalt Dr. Greenland in their brief, claiming, among other things, that he "has been cited as an authority in the *Reference Manual on Scientific Evidence*" and that he co-authored "an authoritative" epidemiology textbook. (Pls.' Br. at 22; *see also id.* at 2.) But they fail to mention Dr. Greenland's role in this litigation (which began before the *Nature* comment was published).

74 (*Id.* at 22 (quoting Amrhein 2019).)

"not advocat[e] a ban on *P* values, confidence intervals or other statistical measures," only that these statistical tools should not be treated "categorically."[75]

Plaintiffs additionally argue that "Professor Hill himself" "condemned" the use of statistical significance, but this argument is based on a deliberate misrepresentation of what Hill actually said.[76] Specifically, plaintiffs quote Hill as stating that "[n]o formal tests of significance can answer these questions . . . they contribute nothing to the 'proof' of our hypothesis."[77] But Hill's full statement was: "No formal tests of significance can answer those questions. ***Such tests can, and, should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that*** they contribute nothing to the "proof" of our hypothesis."[78] In other words, in the portion of the statement plaintiffs intentionally omitted from their brief, Hill explained that testing for statistical significance "***should***" be used to discern the

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[75] Amrhein 2019 at 306; *see also* Wasserstein 2019 at 1, 2, 6 (explaining that "[d]espite the limitations of *p*-values . . . we are not recommending that the calculation and use of continuous *p*-values be discontinued" and offering suggestions for the "thoughtful use and interpretation of *p*-values"); Oleckno 2008 at 224 ("In conclusion, confidence intervals, and to a lesser extent p-values, ***can*** be used to assess random error in study findings.") (emphasis omitted).

[76] (*See* Pls.' Br. at 18, 25-26.)

[77] (*Id.* at 25-26 (citing Hill 1965 at 299).) By "these questions," Hill was referring to the Bradford Hill factors collectively. *See* Hill 1965 at 299.

[78] Hill 1965 at 299 (emphasis added).

degree to which associations reported in studies could be attributable to chance, and therefore spurious. This is the opposite of an "admonition against 'significance testing'" and instead is a reminder of the central role it can play in a causation analysis.[79] In short, the authors of the articles plaintiffs cite generally recommended much more nuanced approaches to considering statistical significance than the outright rejection plaintiffs portray.[80]

Moreover, the approach actually recommended in the articles touted by plaintiffs – essentially, a flexible approach that does not automatically consider non-significant results equivalent to null results – is consistent with the way defendants' experts utilized statistical significance when considering whether there is a consistency of association. As explained above, defendants' experts observed that cohort studies and case-control studies were highly inconsistent – not simply because the former were all non-significant, but because the cohort studies' non-

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[79] (*See* Pls.' Br. at 26.) Plaintiffs also assert that Bradford Hill "further lamented in 1965 that some epidemiologists continued to erroneously apply significance testing, as J&J's experts do here." (*See* Pls.' Br. at 26 (citing Hill 1965 at 299).) Not so. Hill argued in his 1965 address that tests for statistical significance should not be used rigidly, specifically criticizing some journals' practice of rejecting articles that did not test for significance and cautioning that "'no difference'" and "'no significant difference'" do not mean the same thing. Hill 1965 at 299-300. These practices have nothing to do with defendants' experts' methodologies, as explained herein.

[80] To the extent these articles in fact advocated doing away with statistical significance, that position has not come close to gaining general acceptance, as explained above.

significant point estimates were all below or barely above 1.0.[81] Even the authors who criticize the use of statistical significance do not argue that non-statistically significant results that barely exceed 1.0 should be deemed consistent with a finding of causality. To the contrary, these authors explicitly did "***not advocat[e] for an anything goes situation, in which weak evidence suddenly becomes credible***";[82] yet, that is precisely the approach taken by plaintiffs' experts who deemed all of the talc studies consistent without regard for whether they were statistically significant or had divergent risk magnitudes.[83]

In sum, plaintiffs' arguments regarding statistical significance attack straw-man methodologies that defendants' experts did not employ and call for an outright ban on significance testing that even their own authors have not proposed and that has certainly not achieved general acceptance. The Court should deny their request to exclude defendants' experts on this basis.

2. Plaintiffs' And Their Experts' Rejection Of The Established Hierarchy Of Scientific Evidence Renders Them Outliers.

Plaintiffs' arguments disputing the applicability of the well-established hierarchy of scientific evidence are also meritless.

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81 (*E.g.*, Ballman Rep. at 25-26.)

82 Amrhein 2019 at 306 (emphasis added).

83 (*See* General Causation Br. at 47-50.)

First, plaintiffs are wrong insofar as they deny that there is an established hierarchy of scientific evidence that generally ranks cohort studies above case-control studies.[84] Plaintiffs variously argue that defendants' experts' statements that there is a "so-called 'hierarchy of evidence'" are "thinly supported" and based on defendants' experts' "conclusory statements" and "ipse dixit."[85] This contention cannot be taken seriously. The hierarchy of evidence ***is*** generally accepted by the scientific community, and plaintiffs' and their experts' contrary position is the outlier, as fully set forth in defendants' General Causation Brief.[86]

For example, the Oleckno textbook that plaintiffs repeatedly cite in their briefing "ranks the most common types of epidemiologic studies in descending order of the degree to which identical findings of a statistical association are likely

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[84] Plaintiffs also claim that defendants' experts unreliably treated hospital-based case-control studies as more valuable than population-based case-control studies. (Pls.' Br. at 14-15, 31.) But that is not the case. Although defendants' experts pointed out that hospital-based studies "may be less distorted by recall bias than population-based studies because the former feature both ill cases and ill controls" (Diette Rep. at 19 (agreeing with plaintiffs' expert Dr. McTiernan on this point)), they did not take a position as to whether either type of case-control study is generally more reliable. They did point out that hospital-based and population-based case-control studies diverged in terms of reaching statistical significance, but as explained herein, that was not an improper consideration, and in any event was far from the only factor they considered in evaluating whether the talc data show consistency of association.

[85] (Pls.' Br. at 29-30, 31-32.)

[86] (*See* General Causation Br. at 9-12 (explaining the hierarchy and collecting sources).)

to demonstrate a causal association" "based on the relative probability of encountering unrecognized bias, confounding, or other errors within the specific study designs."[87] Its "rank[ing]" of the various study designs is, in pertinent part, as follows: "1. Randomized Controlled Trial"; "2. Group Randomized Trial"; "3. ***Prospective Cohort Study***"; "4. Retrospective Cohort Study"; "5. ***Case-Control Study***."[88] In addition, a World Cancer Research Fund ("WCRF") panel on which plaintiffs' expert Dr. McTiernan sits has published that "[t]he hierarchy of epidemiological evidence places cohort studies above case-control studies" and that "[c]ohort studies are likely to be the main source of evidence" due in part to their prospective design.[89]

Moreover, the talc studies on which plaintiffs and their experts rely recognize that cohort studies are generally regarded as stronger in design than

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87 Oleckno 2008 at 190 (cited in Pls.' Br. at 27, 49, 50, 58).

88 *Id.* (emphasis added).

89 World Cancer Res. Fund & Am. Inst. for Cancer Res., *Continuous Update Project Expert Report: Judging the Evidence* at 7 (2018) (attached as Ex. A153 to Tersigni Cert.). This publication, which sets forth the "systematic and rigorous" approach the WCRF takes when making "evidence-based recommendations" on public health issues, additionally states that when issuing advisories on health issues, the WCRF's research strategy entails looking for randomized controlled trials and cohort studies; "[b]ecause case-control studies are particularly prone to recall (and other) bias, they [a]re ***not routinely reviewed***." *Id.* at 5, 21 (emphasis added and omitted); *see also, e.g.*, Center for Evidence-Based Management, *What are the levels of evidence?*, https://www.cebma.org/faq/what-are-the-levels-of-evidence/ (last visited May 1, 2019) (attached as Ex. A19 to Tersigni Cert.).

case-control studies, stating, for example, that case-control studies are "low-level evidence"[90] and that prospective studies such as cohort studies "are given greater weight" because they are "less prone to bias than case-control studies."[91] And some of plaintiffs' experts have themselves conceded that "typically, the cohort study is ranked as a stronger study design."[92]

Courts have likewise recognized the generally accepted view that there is a hierarchy of evidence that ranks cohort studies above case-control studies. *See Carl v. Johnson & Johnson*, Nos. ATL-L-6546-14, ATL-L-6540-14, 2016 WL 4580145, at *12, *19 (N.J. Super. Ct. Law Div. Sept. 2, 2016) (explaining that case-control studies "are considered less reliable than a prospective cohort study" and excluding plaintiffs' experts who relied on case-control studies to conclude that talc use causes ovarian cancer but "looked askance upon the three large cohort studies presented by [d]efendants"), *appeal pending*; *Planned Parenthood Fed'n of Am. v. Ashcroft*, 320 F. Supp. 2d 957, 985 (N.D. Cal. 2004) (recognizing that

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90 Penninkilampi & Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*, 29 Epidemiol. 41, 47 (2018) ("Penninkilampi 2018") at 47 (attached as Ex. A109 to Tersigni Cert.).

91 Narod 2016 at 2 (emphasis added).

92 (Dep. of Patricia G. Moorman, M.S.P.H., Ph.D. ("Moorman Dep.") 301:21-302:4, Jan. 25, 2019 (attached as Ex. B39 to Tersigni Cert.); *see also* Smith-Bindman Rep. at 16 ("The commonly held view is that cohort studies are better than case-control studies.").)

"[r]esearch methodology is evaluated on a hierarchy," with prospective studies ranking above retrospective studies), *aff'd sub nom. Planned Parenthood Fed'n of Am., Inc. v. Gonzales*, 435 F.3d 1163 (9th Cir. 2006), *rev'd on other grounds sub nom. Gonzales v. Carhart*, 550 U.S. 124 (2007).[93] Plaintiffs point to no contrary case law.

Finally, the sources plaintiffs do cite to challenge the existence of an evidentiary hierarchy – which were nearly exclusively written by one person, Dr. Kenneth Rothman – presuppose that a generally accepted hierarchy of evidence exists in seeking to challenge the "'[c]onventional wisdom" that case-control studies are inferior to cohort studies.[94] These sources accordingly only show that

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[93] *See also Fleminger, Inc. v. U.S. Dep't of Health & Human Servs.*, 854 F. Supp. 2d 192, 212 (D. Conn. 2012) (agreeing with the FDA that the "case-control study method" is "weaker as it is susceptible to more forms of bias [than] prospectively designed studies"); *Hennessey v. Sec'y of Dep't of Health & Human Servs.*, No. 01-190V, 2009 WL 1709053, at *28 (Fed. Cl. May 29, 2009) ("Cohort studies are more precise than case control studies, because they are prospective in nature. Over a period of years, they may find that small levels of exposure have an effect.").

[94] (*See* Pls.' Br. at 35 (citing Rothman et al., *Modern Epidemiology* 111 (3d ed. 2008) ("Rothman 2008"), which argues against the consensus that case-control studies "do not yield estimates of effect that are as valid as measures from cohort studies"); *see also id.* at 36 (quoting Rothman's acknowledgment that it is "commonly believed that the validity of case-control studies is worse than cohort studies") (emphasis omitted); *id.* at 26 (quoting Rothman's statement about a "common" approach to consistency that he disagrees with); *id.* at 28 (quoting Rothman's statement about an alleged "low road [that] is crowded with others taking the same path" with respect to statistical significance).) Of note, despite

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"conventional wisdom" ***does*** generally regard cohort studies as providing more reliable evidence of causation than case-control studies. In any event, Rothman's arguments, even if accepted, do not undermine the approach defendants' experts took here. Rather, he merely argues that researchers should holistically consider the quality of study design and all available data – and that "discrepancies between cohort studies and case-control studies should not be explained away superficially by a presumed validity advantage for cohort studies over case-control studies."[95] As explained above, defendants' experts have not premised their opinions solely on the presumption that cohort studies occupy a higher position on the hierarchy of evidence than case-control studies.

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heavily relying on Dr. Rothman throughout their brief, plaintiffs ignore that when he specifically evaluated the relationship between talc and ovarian cancer, he concluded that a causal relationship had ***not been established***. *See* Rothman et al., *Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer* at 1 (2000) (attached as Ex. A126 to Tersigni Cert.) (concluding that "the evidence to date does not indicate that talc can be 'reasonably anticipated to be a human carcinogen'" and that either recall bias or confounding could "readily" or "easily" account for the "overall weak association of a relative risk of 1.31" in case-control studies).

[95] *See* Rothman 2014 at 1061.

For all of these reasons, plaintiffs' attack on the "fundamental principle of evidence-based medicine" that scientific evidence "is hierarchical"[96] is baseless.

Second, although the evidentiary hierarchy is a general principle that is subject to exceptions, plaintiffs and their experts lack a reliable basis for contending that such exceptions exist here, i.e., that the talc case-control studies specifically are more reliable than the talc cohort studies. Indeed, even plaintiffs' sources – which generally argue that individual case-control studies can be on par with or better than individual cohort studies depending on design – say nothing about the relative value of the ***talc*** cohort and case-control studies in particular.[97] By contrast, published articles that have specifically considered talc cohort and case-control studies have found – in the case of one such article co-authored by plaintiffs' expert Dr. Jack Siemiatycki, for example – that a cohort study was

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[96] Wong et al., Fed. Judicial Ctr., *Reference Guide on Medical Testimony, in Reference Manual on Scientific Evidence* 687, 723 (3d ed. 2011) (attached as Ex. A175 to Suppl. Tersigni Cert.).

[97] *E.g.*, Rothman 2014 at 1060-61 (discussing the hierarchy of evidence between cohort and case-control studies generally and only referring to two specific examples – studies on cigarette smoking and coronary heart disease); Vandenbroucke, *Observational research and evidence-based medicine: what should we teach young physicians?*, 51(6) J Clin Epidemiol. 467 (1998) (attached as Ex. 69 to Pls.' Br.) (discussing general research principles and not discussing talc).

"arguably the strongest study because of its partly prospective ascertainment of exposure."[98]

Consistent with this approach, defendants' experts began with the premise that cohort studies are "generally" considered more accurate than case-control studies,[99] and then considered whether studies specific to talc are an exception.[100] For example, Dr. Ballman explained her approach as follows:

> As between these two types of observational data, the level of evidence for establishing causality is greater for prospective cohort studies . . . . As indicated, prospective cohort studies minimize biases such as recall bias and participant selection bias, which is why they have a higher level of evidence than case-control studies. Based on my experience, there needs to be overwhelming and

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98 Langseth et al., *Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiology & Cmty. Health 358, 358 (2008) (attached as Ex. A88 to Tersigni Cert.) ("Langseth 2008") (meta-analysis further explaining that "the influence of . . . recall bias cannot be ruled out" in case-control studies).

99 (*E.g.*, Merlo Rep. at 27 ("In general, cohort studies provide more evidence for a causal relationship between exposure and outcome and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if the design, conduct, data collection and analysis are proper."); Ballman Rep. at 7 ("Generally, in my experience, prospective cohort studies yield a higher level of evidence than case-control studies.").)

100 As Dr. Merlo explains, plaintiffs' experts extensively criticized the cohort studies but glossed over the significant (and more severe) flaws in the case-control studies. (Merlo Rep. at 27 ("While cohort studies also have their own limitations like any other study design, the focused criticism of cohort studies by plaintiffs' epidemiologists, even though they are generally considered more reliable than case-control studies, suggests a biased approach to their analysis."); *see also* General Causation Br. at 47-50.)

> compelling evidence to overcome the scientific consensus and conclude that case-control studies offer a higher level of evidence. Absent such compelling circumstances, if there is a conflict in results between prospective cohort studies and case-control studies, it is scientifically justified to place more weight on the results from the prospective cohort studies, since they have fewer biases than case-control studies.[101]

Dr. Merlo similarly explained:

> Consistent with [the] hierarchy, epidemiologists consider meta-analyses of multiple randomized clinical trials, followed by individual randomized clinical trials, as the strongest evidence to support a causal relationship between an exposure and an outcome. These are followed by the observational designs, with cohort studies, case-control studies, and cross-sectional studies in descending order also providing potential evidence for a causal association between exposure and outcome. . . . As a general rule, lower-quality studies provide less information on whether a causal relationship exists than studies of higher quality.
>
> Although this hierarchy should ***not be indiscriminately applied*** to all research questions and studies, an epidemiologist should provide sound scientific justifications for departing from these well-established norms.[102]

Applying these principles, defendants' experts concluded that all of the talc studies have limitations, but there are no sound reasons to elevate the case-control studies over the cohort studies as plaintiffs' experts do. In reaching this conclusion,

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101 (Ballman Rep. at 15.)

102 (Merlo Rep. at 35 (emphasis added).)

defendants' experts considered plaintiffs' experts' numerous attacks on the validity of the talc cohort studies, including that the cohort studies lack adequate size and power, did not follow participants long enough and potentially mischaracterized participants as talc users or nonusers.[103] Defendants' experts concluded that these arguments are, among other things, speculative, circular and dependent on incorrect math, and that they do not show that the hierarchy of evidence does not apply to the talc literature.[104]

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[103] (*See* General Causation Br. at 76.) Plaintiffs are accordingly wrong in arguing that alleged "'[m]isclassification bias'" in the cohort studies was "dismissed by J&J's experts." (Pls.' Br. at 46.) Specifically, defendants' experts explained that the theoretical misclassification of talc users and nonusers is unlikely to have significantly occurred or materially affected the accuracy of the cohort studies. (Ballman Rep. at 7-8.)

[104] (*See, e.g.*, Ballman Rep. at 7-8, 26-28; Diette Rep. at 10-11, 30; Merlo Rep. at 37-39; *see generally* General Causation Br.) Although plaintiffs' experts focused on criticizing only the cohort studies, defendants' experts explained that there is direct evidence that inherent weaknesses in case-control studies that prompt scientists to "generally" consider them less valuable than cohort studies – i.e., unique susceptibility to recall bias and confounding – ***in fact*** are at play here. Specifically, the Schildkraut 2016 study reported that women who were likely to have heard about the talc controversy from the media were more likely to report increased talc use, which is strong evidence of recall bias. (Diette Rep. at 19-20; Ballman Rep. at 52; Merlo Rep. at 7.) Defendants' experts further explained that case-control studies are more likely to produce spurious associations from both known and unknown confounding variables, and that the talc case-control studies did not uniformly control for such variables. (Ballman Rep. at 6-7, 26; Diette Rep. at 20-21; Merlo Rep. at 13.) In particular, they pointed out that douching, "an exposure not considered in nearly all other studies," was found to be both a risk factor for ovarian cancer in a recent cohort study and correlated with talc use and thus a potential source of confounding. (Diette Rep. at 21; Merlo Rep. at 7-8.)

In short, the sources plaintiffs cite in challenging the well-accepted hierarchy of evidence merely point out that the hierarchy is subject to exceptions – they do not show that the talc case-control studies are those exceptions. As defendants and their experts have explained, although all the talc studies have limitations, ***plaintiffs' experts*** are the ones who have taken the outlier position that the flawed case-control studies provide strong evidence while the less-flawed cohort studies should be ignored.[105] This, not defendants' experts' approach, was unreliable.

II. DEFENDANTS' EXPERTS RELIABLY CONSIDERED DOSE RESPONSE AND BIOLOGICAL PLAUSIBILITY.

A. Defendants' Experts Did Not "Misstate And Misapply The Biologic Gradient (Dose Response) Aspect Of Bradford Hill."

Plaintiffs contend that defendants' experts did not reliably consider whether evidence of a dose response supports causation, and that their opinions on this issue do not "'fit' the facts of this case," because they "applied a heightened – and incorrect – definition for this Hill aspect."[106] According to plaintiffs, defendants' experts erred because they "required" evidence of a dose response to support a causal inference, when, in plaintiffs' view, evidence of a dose response is "unnecessary."[107] Plaintiffs propose that the proper way to assess dose response is

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105 (*See, e.g.*, Diette Rep. at 11; General Causation Br. at 47-50.)

106 (Pls.' Br. at 56-57.)

107 (*Id.* at 52.)

to ask whether there is "*any* evidence of *any* kind which would support a dose-response relationship."[108] And if there is no such evidence, plaintiffs believe that the proper course is not to consider this factor as weighing against a causal inference like defendants' experts did, but instead to ignore it altogether and look to other Bradford Hill factors.[109]

It is unsurprising that plaintiffs seek to define the dose-response criterion in a way that essentially permits it to be bypassed given that a number of their own experts concede that the relevant evidence is "equivocal," "inconsistent," "less compelling" and should be "given [] lesser weight" in the causation analysis.[110]

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108 (*Id.* at 51.)

109 (*Id.* ("If not, other Hill aspects should be considered . . . .").)

110 (*See, e.g.*, Kane Rep. at 35 ("equivocal"); Singh Rep. at 65 ("less compelling"); Smith-Bindman Rep. at 40 ("inconsistent"); Expert Report of Judith Wolf, M.D. at 15, Nov. 16, 2018 (attached as Ex. C23 to Tersigni Cert.) ("less important factor"); *see also* Expert Report of Dr. Ghassan M. Saed at 11, Nov. 16, 2018 (attached as Ex. C17 to Tersigni Cert.) (observing that the epidemiological studies "have shown conflicting results regarding the presence of a dose-response, largely due to the failure of many studies to obtain necessary information on the frequency and duration of usage and the inherent challenge of quantifying actual exposure"); Dep. of Jack Siemiatycki, Ph.D. 123:8-14, Jan. 31, 2019 (attached as Ex. B29 to Tersigni Cert.) (agreeing that the data are "compatible with no dose-response relationship"; "it could be a chance finding"); Smith Rep. at 20 (additional research needed to "help clarify dose response relationships"); Expert Report of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Rep.") at 9, Nov. 16, 2018 (attached as Ex. C14 to Tersigni Cert.) (calling for molecular research to "elucidate" dose response).)

But plaintiffs' unscientific attempt to delete dose response from the Bradford Hill framework is obviously no basis for excluding defendants' epidemiology experts.

In arguing that dose response is "not a necessary element" of a causal inference, plaintiffs principally rely on Hill's original description of the dose-response criterion, in which he acknowledged that it may be "difficult[] . . . to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose response."[111] But in the passage plaintiffs quote, Hill stated that scientists "***should invariably seek***" evidence of a dose response.[112] Moreover, a number of courts have disagreed with plaintiffs' proposed approach, holding that considering "dose-response relationship is a ***key element*** of reliability in toxic tort cases." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1241 n.6, 1242 (11th Cir. 2005) (emphasis added); *Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1308 (11th Cir. 2014) (a dose response is "indispensable to proving the effect of an ingested substance" and "establish[ing] general causation"). Courts accordingly exclude experts purporting to infer causation despite a "lack of any demonstrated dose-response relationship." *Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 778 (D. Md. 2002) (excluding causation expert in part because of

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111 (Pls.' Br. at 50 (emphasis omitted) (quoting Hill 1965).)

112 (*Id.* (quoting Hill 1965 at 298).) In additional language that plaintiffs omit, Hill stated that evidence of a dose response should be "envisage[d]" in order to "satisfy the cause-and effect hypothesis." Hill 1965 at 298.

the "lack of any demonstrated dose-response relationship" between cell phone use and brain cancer), *aff'd*, 78 F. App'x 292 (4th Cir. 2003) (per curiam); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 515 (W.D. Pa. 2003) (excluding experts where "[n]o dose response relationship for Parlodel and the occurrence of Intracerebral hemorrhage ha[d] been documented") (citation omitted).[113]

Defendants do not dispute that in some instances, the evidence regarding dose response may be non-existent or too attenuated to weigh in favor of, or against, a causal inference. That was so in the cases plaintiffs cite.[114] For example, in *In re Avandia Marketing, Sales Practices & Products Liability Litigation*, No. 2007-MD-1871, 2011 WL 13576 (E.D. Pa. Jan. 4, 2011), the court held that causation testimony that did not consider dose response was admissible "because there was little variation in the prescribed doses" of the drug, and dose response accordingly "could not [be] assess[ed]." *Id.* at *9, *14. And far from holding that evidence of dose response is "unnecessary," the court in *Stand 'N Seal Products Liability Litigation*, 623 F. Supp. 2d 1355 (N.D. Ga. 2009), stated that an expert who "avoids or neglects [dose response] without justification ***casts suspicion on the reliability of his methodology***." *Id.* at 1373 (emphasis added) (citation

[113] Plaintiffs' expert Dr. Siemiatycki recognizes that "[a]n important part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern." (Siemiatycki Rep. at 42.)

[114] (*See* Pls.' Br. at 50-51.)

omitted). The court held, however, that the expert there did provide sufficient "justification" for not significantly considering dose response because he "relied on all of the [other Bradford Hill] factors" where studies did not provide useful information on dose. *Id.*[115]

The situation here is different. Although plaintiffs' and defendants' experts broadly agree that talc studies have not been able to accurately measure participants' talc exposure, a large number of studies have nevertheless reported on dose trends (or lack thereof) by considering the frequency, duration or the combined frequency and duration of women's talc use. As explained in defendants' General Causation Brief, these studies have overwhelmingly failed to show evidence of a dose response – a conclusion that numerous third-party scientists have recognized, including the authors of the Health Canada Draft Assessment.[116]

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[115] *Rowland v. Novartis Pharmaceuticals Corp.*, 9 F. Supp. 3d 553, 564 (W.D. Pa. 2014) (cited in Pls.' Br. at 54), is likewise inapposite because it did not address the showing needed when considering the dose-response Bradford Hill factor, but rather whether a certain study supported an expert's testimony (not based on Bradford Hill or a similar methodology) regarding the efficacy and risk of lowering the dose of a drug.

[116] (General Causation Br. at 68.) Indeed, as noted above, the Health Canada Draft Screening Assessment – which plaintiffs rely on throughout their brief, but not in the sections discussing dose response – reported that even among "studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc," "***none demonstrate both a clear dose-response trend and statistical significance***." Draft Screening Assessment at 20-21 (emphasis added); *see also, e.g.*, Langseth 2008 at 359 (meta-analysis co-authored by Dr.

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And while a number of plaintiffs' experts focus on a cherry-picked subset of studies (and often, only particular data within those studies) to attempt to glean evidence of a dose response, this exercise itself shows that plaintiffs' own experts do not agree that evidence of a dose response is "unnecessary."[117]

By contrast, defendants' experts have shown that even the studies plaintiffs' experts believe provide the strongest indication of a dose response instead refute plaintiffs' theory.[118] In particular, plaintiffs' experts generally consider the Terry

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Siemiatycki explaining that a crucial missing piece of causation evidence was "***the absence of clear exposure response associations in most studies***.") (emphasis added); Letter from Steven M. Musser, Ph.D., Deputy Dir. for Sci. Operations, Ctr. for Food Safety & Applied Nutrition, to Samuel S. Epstein, M.D., Cancer Prev. Coalition, Univ. of Ill. – Chi. School of Pub. Health, at 4 (Apr. 1, 2014) ("FDA Denial Letter") (attached as Ex. A89 to Tersigni Cert.) (arguing that "dose-response evidence ***is lacking***") (emphasis added); Nat'l Cancer Inst., Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)–Health Professional Version, https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq (last updated Mar. 1, 2019) ("2019 NCI PDQ") (attached as Ex. A104 to Tersigni Cert.) (reporting that "a dose response relationship was not found" and "there was no increased risk observed for increasing duration of use"); Int'l Agency for Research on Cancer, World Health Org., 93 *Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide, and Talc* 412 (2010) (attached as Ex. A72 to Tersigni Cert.) ("inconsistent" evidence of a dose response).

117 (*See* General Causation Br. at 68-75.)

118 (*See, e.g.*, Merlo Rep. at 32 (explaining that the "[s]tudies that have evaluated the potential for dose-response have found: (1) random or 'sine wave' (up and down) risk; (2) convex (up and down) risk; (3) concave (down then up) risk; and (4) even decreasing risk with either increasing frequency or duration of

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2013 pooled study[119] to be the "the most important piece of evidence we have on dose-response."[120] But, as defendants' experts explain, that study showed a dose trend only when non-talc users were improperly included in the analysis, with the Terry authors themselves explaining that a proper assessment of their data showed "***no significant trend in risk with increasing number of lifetime applications***."[121] Defendants' experts further explained that a different study that plaintiffs' experts rely on (Cramer 2016) identified "no clear pattern suggesting a dose-response effect," and instead "a random sine wave pattern with increasing risk, then decreasing risk, then increasing risk with total genital talc applications."[122] And

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talc use") (citations omitted); Diette Rep. at 29 ("the findings of so many different patterns, or lack of patterns, by dose-response estimation weighs against causation").)

[119] Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*, 6(8) Cancer Prevention Res. 811 (2013) ("Terry 2013") (attached as Ex. A139 to Tersigni Cert.).

[120] (Siemiatycki Rep. at 45; *see also* Expert Report of Anne McTiernan M.D., Ph.D. ("McTiernan Rep.") at 55, Nov. 16, 2019 (attached as Ex. C7 to Tersigni Cert.) (considering Terry 2013 to be "strong evidence" of causation because "the dose-response effect was clear"); Smith-Bindman Rep. at 28 (opining that "[a] significant dose response was seen" in Terry 2013).)

[121] (Diette Rep. at 28 (citing Terry 2013 at 811 (abstract)); Ballman Rep. at 29-30 (explaining that "[i]t is important to limit the [dose response] analysis to only those users of perineal talcum powder" because otherwise, the data "could just again be a measure of ever use versus never use").)

[122] (Merlo Rep. at 24, 32 (discussing Cramer 2016 at 336-37 tbl. 1); *see also* Dep. of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Dep.") 192:12-14, Nov.

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similar concerns make it impossible to identify a true dose response in the other studies or meta-analyses relied on by several of plaintiffs' experts.[123] In short, this is not a situation where there are no data on dose response; rather, the data are simply not favorable to plaintiffs' positions. And plaintiffs' experts' desperate attempts to conjure a dose response from the relevant studies suggest that even they do not really believe that the dose-response consideration should simply be ignored.

Finally, plaintiffs' contention that "*any* evidence of *any* kind" may be considered in determining whether data indicate a dose response[124] does not justify the conclusion that experts may use a single study or tiny subset of studies to "check the box" on dose response without considering whether the totality of the data actually support the existence of a dose response. Plaintiffs' only case for their "any evidence" standard – *In re Tylenol (Acetaminophen) Marketing, Sales*

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16, 2018 (attached as Ex. B10 to Tersigni Cert.) (admitting "[t]here is not a consistent dose response" in Cramer 2016).)

[123] (*See, e.g.*, Diette Rep. at 29 (explaining that the Berge 2018, Schildkraut 2016 and Penninkilampi 2018 studies did not show convincing evidence of a dose response because the Berge 2018 "data came from a small number of case-control studies" and the Schildkraut 2016 and Penninkilampi 2018 articles utilized an "arbitrary dichotomous categorization of lifetime use"); Ballman Rep. at 34-35 (explaining that dose trend observed in Berge 2018 and Penninkilampi 2018 "may be driven by the association between ever use and never use").)

[124] (*See* Pls.' Br. at 51.)

Practices, & Products Liability Litigation, No. 2:12-cv-07263, MDL No. 2436, 2016 WL 3997046 (E.D. Pa. July 26, 2016) – says no such thing, and in fact did not comment on the quality of evidence needed to evaluate the dose-response criterion, or even consider expert testimony based on the Bradford Hill methodology. *Id.* at *5-7 & n.20 (finding that an expert appropriately relied on, *inter alia*, case reports and his own experience where there were no epidemiological studies; noting that the expert did not purport to apply the Bradford Hill criteria). Meanwhile, other courts have explained that experts must "lay a 'reliable groundwork for determining the dose-response relationship.'" *Williams v. Mosaic Fertilizer, LLC*, 889 F.3d 1239, 1248 (11th Cir. 2018) (citation omitted); *see also In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1353 (S.D. Fla. 2011) (requiring "dose-response evidence which [p]laintiffs' experts may use to reliably infer what type of exposure level to [the product] is necessary to induce [injury]"); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 188 (E.D.N.Y. 2001) (excluding general causation expert who cited literature in which "[f]ew, if any, dose-response relationships were reported"), *aff'd*, 303 F.3d 256 (2d Cir. 2002). In other words, although the precise level of evidence needed to deem the dose-response factor supportive of causation may depend on the particular facts, there is no support in science or the law for the notion that an expert may move on to other Bradford Hill factors the moment "*any*

evidence of *any* kind" has been identified that could possibly support a dose response.[125]

In sum, although plaintiffs criticize defendants' experts for not "provid[ing] *any* support whatsoever for [their] . . . re-definition of dose response,"[126] plaintiffs have attempted to define the dose-response criterion in an unsupported and unscientific way, and it is their experts who failed to analyze this factor reliably.

B. Defendants' Experts Did Not "Misstate And Misapply The Biologic Plausibility Aspect Of Bradford Hill."

Plaintiffs also argue that defendants' experts' opinions with respect to biological plausibility are unreliable. According to plaintiffs, Drs. Diette and Ballman applied too exacting a standard for biological plausibility by "**conflat[ing it] with biologic proof**."[127] They further assert that Drs. Diette and Ballman failed to consider whether the alleged presence of "potential carcinogens like asbestos or

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125 Plaintiffs' criticism of Dr. Ballman for considering the consistency of the reported dose-response associations (Pls.' Br. at 51-53) is disingenuous given that some of plaintiffs' own experts assessed dose response in this manner (*see* Smith-Bindman Rep. at 40 ("most but not all studies of talcum powder products and ovarian cancer show a dose response, but the results are inconsistent, and more importantly, are not considered or assessed in most of the published studies"); Moorman Rep. at 31 (opining that dose-response "observations are less consistent than the overall association")).

126 (Pls.' Br. at 53.)

127 (*Id.* at 57-60.)

fibrous talc" would supply a plausible biological mechanism through which talc use can cause ovarian cancer.[128] These arguments, too, should be rejected.

First, plaintiffs are incorrect that defendants' experts applied too stringent a test for biological plausibility. And even if plaintiffs' definition were accurate – that a biological plausibility theory must only "make sense"[129] – defendants' experts have reliably shown that plaintiffs' experts' opinions would not satisfy that lesser standard.

Courts have explained that a biological plausibility theory cannot be "merely an unproven hypothesis" unsupported by "evidence of [how] the mechanism . . . works," *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007), and that a "proposed mechanism" must be "substantiated by scientific evidence." *Soldo v. Sandoz Pharm. Corp.*, No. 98-1712, 2003 WL 22005007, at *4 (W.D. Pa. Jan. 1, 2003); *see also In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 616 (E.D. La. 2003) (excluding experts who "have left too great a gap in their theory of biologic plausibility to support their arguments"). As the *Zoloft* case explained, an expert opining on biological plausibility may not "testify to an untested hypothesis," and instead must invoke biological pathways with a "well

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128 (*Id.* at 57, 61.)

129 (*Id.* at 58-60.)

established effect." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 473 (E.D. Pa. 2014) (citation omitted) (cited in Pls.' Br. at 59).[130]

Moreover, scientists and courts have explained that in cases such as this, where "scholarship has *not* shown more than a correlation, subject to identifiable confounders, between [the product and the disease]," "it is not enough" "for an expert as to general causation to opine that a biological pathway exists but is not well understood." *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 286 (S.D.N.Y. 2018).[131] Consistent with these principles, the court in *Carl* excluded plaintiffs' causation experts' opinions in part on the ground that they "fail[ed] to provide a coherent explanation to support their hypothesis for

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[130] Plaintiffs' remaining cases do not impose a different standard because they stop short of delineating the specific level of evidence needed to reliably opine on biological plausibility. *See Bartoli v. Novartis Pharm. Corp.*, No. 3:13-0724, 2014 WL 1515870, at *8 (M.D. Pa. Apr. 17, 2014) (stating that hypotheses that "ha[v]e been deemed plausible and credible in the relevant medical literature" may be admissible) (citation omitted); *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, Nos. 11-5304, 08-08, 2013 WL 1558690, at *3 (D.N.J. Apr. 10, 2013) (defining, without providing any analysis, biological plausibility as "coherence with existing knowledge") (both cited in Pls.' Br. at 59-60).

[131] *See also* Wynder et al., *Weak Associations in Epidemiology and Their Interpretation*, 11 Preventive Med. 464, 465 (1982) ("Wynder 1982") (attached as Ex. A157 to Tersigni Cert.) (explaining that "the need to seek supporting evidence is greater with weak than with strong associations"); Green et al., Fed. Judicial Ctr., *Reference Guide on Epidemiology, in Reference Manual on Scientific Evidence* 549, 602 (3d ed. 2011) ("Epidemiology Reference Manual") (attached as Ex. A51 to Tersigni Cert.) (explaining that "epidemiologist[s] will scrutinize [weak] associations more closely").

biologic plausibility." 2016 WL 4580145, at *12. As Judge Johnson explained, the experts failed to articulate "what it is about talc in the ovaries . . . that sets off a chain of events which purportedly causes ovarian cancer," and merely "[u]ttering the term inflammation does not explain the etiology of ovarian cancer." *Id.* at *14, *21. These are the same criticisms of the same theories and opinions that are included in Drs. Ballman and Diette's reports.

As these experts explained:

- Numerous talc studies have found that "the evidence is insufficient to understand any purported mechanism by which talc-based cosmetic powders could cause ovarian cancer."[132] In addition, "although there is some evidence for individual components of the proposed process . . . there is no demonstration for the entire process from perineal/genital talcum powder exposure to the development of ovarian cancer that has been proposed."[133]

- The data are inconclusive on whether talc or asbestos particles can travel from the perineum to the ovaries, as Dr. Diette put it, "against gravity and the downward flow of vaginal mucous and menstrual fluids."[134] In particular, research showing that talc particles have been found in women's ovaries is "of no scientific significance because researchers have found such particles in the ovaries of women with

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[132] (Diette Rep. at 36-37 (citing numerous studies, including Penninkilampi 2018 and Berge 2018).)

[133] (Ballman Rep. at 37.)

[134] (Diette Rep. at 38; Ballman Rep. at 37 ("What is missing is evidence that sufficient quantities of talcum particles from perineal/genital application migrate to the fallopian tubes and ovaries to cause chronic inflammation that gives rise to the development of ovarian cancer.").)

and without" known talc exposure.[135] By contrast, studies showing no association between ovarian cancer and the use of talc-dusted diaphragms and condoms (where "'by definition, the female reproductive tract is exposed to talc'") indicate that migration is not plausible.[136] The inconsistent results reached by studies on whether tubal ligation and hysterectomy – which would "prevent the migration of talc particles from the perineum" – reduce ovarian cancer risk in talc users similarly indicate a lack of support for the migration theory.[137] Finally, there is no reliable evidence that inhaled talc particles can reach ovaries.[138]

- Key data that would support the inflammation theory are absent. Most notably, the evidence is "mixed at best" regarding an association between use of anti-inflammatory drugs and a reduced risk of ovarian cancer;[139] there is no evidence that talc causes cancer by way of inflammation in patients who undergo pleurodesis (which, as Dr. Diette explains, "entails the therapeutic injection of talc into the pleural cavity to cause beneficial scarring");[140] and there are "no data of ongoing or chronic inflammation in perineal talc users, whether in the ovary or otherwise, or that inflammation is occurring in the presence of talc in ovarian tissue."[141]

- "[N]o biological mechanism theory accounts for the fact that talc is not mutagenic or genotoxic."[142] And "[t]here are no animal models

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135 (Diette Rep. at 38; Ballman Rep. at 37 (noting that there is no evidence that "only women who use perineal/genital talcum powder have embedded particles in ovary tissue" or that "women who use more talcum powder have a higher risk (and perhaps greater quantity) of embedded particles").)

136 (Diette Rep. at 39 (citation omitted).)

137 (*Id.*)

138 (*Id.* at 40.)

139 (*Id.* at 41-42.)

140 (*Id.* at 42.)

141 (Ballman Rep. at 37.)

142 (Diette Rep. at 40.)

> that demonstrate carcinogenesis from perineal/genital talcum powder application."[143]

In sum, defendants' experts did not apply the wrong standard for biological plausibility, or unreasonably analyze this consideration.

Second, plaintiffs' argument that defendants' experts' opinions regarding biological plausibility should be excluded because they did not consider the role of asbestos or other alleged talc contaminants is meritless for a number of reasons.[144]

As an initial matter, Dr. Diette extensively considered the putative role of asbestos in addressing plaintiffs' experts' biological plausibility opinions[145] elsewhere in his report.[146] Plaintiffs' argument ignores these highly relevant portions of his report.[147] Among other things, Dr. Diette explained that the alleged

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143 (Ballman Rep. at 37.)

144 (*See* Pls.' Br. at 57, 61.)

145 (Diette Rep. at 38-42 (addressing whether asbestos particles can migrate to the ovaries); *see also id.* at 3 ("[p]laintiffs' experts' asbestos-based theories are also problematic due to the lack of a plausible mechanism by which asbestos could reach the ovaries and a lack of any reliable epidemiology supporting such a causal connection").)

146 (*Id.* at 43-47 (explaining, among other things, that there are a lack of reliable and consistent epidemiological studies showing an association between asbestos and ovarian cancer, and that the studies that do exist involved an amount and type of exposure that is not comparable to exposures alleged through talc use).)

147 (Pls.' Br. at 57, 61.) Plaintiffs instead cite a sentence from Dr. Diette's deposition where he stated, in response to a question about content on page 3 of his report, that the talc epidemiological studies "don't break down or don't do analyses of what the talcum powder is or what it consists of" and "whatever is in talcum

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presence of asbestos would not change any aspect of his Bradford Hill analysis "because the existing epidemiological literature regarding perineal talc use would necessarily account for the presence of any asbestos in the products used in those studies."[148] This is consistent with plaintiffs' experts' own admissions on the issue.[149] And Dr. Diette's observation extends to animal and in vitro studies as well, since those studies used talc that, if plaintiffs' theories are correct, would likewise necessarily have included the accessory minerals that they contend are present in the Products.[150]

Moreover, defendants' experts did not need to consider whether the alleged presence of asbestos or other contaminants would inform biological plausibility because plaintiffs have no reliable evidence that defendants' talc products contain allegedly harmful contaminants, let alone that such contamination was at levels

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powder is baked into the epidemiology." (Dep. of Gregory B. Diette, M.D. 77:11-15, Apr. 9, 2019 (attached as Ex. B26 to Tersigni Cert.) (cited in Pls.' Br. at 61).) This statement is an example of Dr. Diette considering, not ignoring, the alleged effect of asbestos.

148 (Diette Rep. at 3, 6.)

149 (*See, e.g.*, Moorman Dep. 124:20-126:6 (stating that her opinion is "based on talcum powder products, whatever is contained them -- in them" and that the alleged presence of asbestos "doesn't change the . . . epidemiologic studies"); Dep. of Sonal Singh, M.D., M.P.H. ("Singh Dep.") 273:6-9, Jan. 16, 2019 (attached as Ex. B47 to Tersigni Cert.) (similar).)

150 (*See* Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts Ops. Related to Biological Plausibility at 19, May 7, 2019 (ECF No. 9736-1).)

that could cause ovarian cancer, as fully set forth in defendants' briefing on those specific issues.[151] Indeed, none of plaintiffs' experts considered whether the amount of asbestos alleged to be present in the Products can cause ovarian cancer.[152] And in alleging that the Products contain asbestos, plaintiffs' epidemiology (and biological plausibility) experts unreliably relied on litigation-driven testing by Drs. William Longo and Mark Rigler and out-of-context documents cherry-picked by plaintiffs' counsel.[153]

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[151] (*See* Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts Asbestos-Related Ops. ("Defs.' Asbestos Br."), May 7, 2019 (ECF No. 9736-3); Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts Ops. Regarding Alleged Heavy Metals & Fragrances in Johnson's Baby Powder and Shower to Shower, May 7, 2019 (ECF No. 9736-4).)

[152] (*See* Defs.' Asbestos Br. at 87.)

[153] (*See, e.g.*, Moorman Rep. at 35 (opining that "[t]here is evidence that products manufactured after 1976 are not asbestos-free," citing "[s]tudies from Longo, et al."); Expert Report of Arch Carson, M.D., Ph.D. ("Carson Rep.") at 5, Nov. 16, 2018 (attached as Ex. C9 to Tersigni Cert.) ("I have seen evidence that Johnson & Johnson's talcum powder products contain asbestos and fibrous talc," citing Dr. Longo's report); Smith Rep. at 18 (same); Siemiatycki Rep. at 29-30 (noting that a "number of labs have reported finding asbestos fibers in talcum powder products," citing two studies by Dr. Longo); Clarke-Pearson Rep. at 6 (opining that "[t]alcum powder also contains other carcinogens including asbestos," citing expert report of Drs. Longo and Rigler); Expert Report of Laura M. Plunkett, Ph.D., DBAT at 20-21, Nov. 16, 2018 (attached as Ex. C28 to Tersigni Cert.) ("In more recent work related to this litigation, scientists have found that samples of Johnson & Johnson body powder products that were examined contained fibrous talc," citing testing by Longo & Rigler).)

For all of these reasons, defendants' experts' opinions regarding biological plausibility were reliable, and plaintiffs' motion should be denied on this ground as well.

III. DR. MERLO'S ANALYSIS WAS METHODOLOGICALLY SOUND AND COMPLETE.

Plaintiffs additionally argue that Dr. Merlo's opinions should be excluded because he "did not perform a complete causation analysis" and "committed serious methodological errors by not considering" all of the "considerations under the Bradford Hill analysis."[154] But Dr. Merlo's approach was sound because biological plausibility alone would not suffice to prove causation under these circumstances. As he explained: "[W]ith a lack of strength of association, with a lack of consistency between studies and with a lack of dose response, biologic plausibility doesn't matter because there's no causal association between talcum powder and ovarian cancer based on the medical literature."[155]

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154 (Pls.' Br. at 65-66; *see also id.* at 57 n.122.)

155 (Merlo Dep. 178:24-179:5.) Dr. Merlo also explained that a "predicate of a Bradford Hill analysis" is that studies "'reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance.'" (Merlo Rep. at 30 (quoting Hill 1965 at 295).) He explained that "this requirement is likely not satisfied here." (*Id.*) Plaintiffs criticize this opinion as being "at odds with the published literature that has been published outside of litigation," principally citing an editorial that disagreed that "'there is no evidence that talc is associated with ovarian cancer.'" (Pls.' Br. at 32 & n.69 (citing Narod 2016).) But this does not make Dr. Merlo's opinion unreliable given that the

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Plaintiffs' motion should accordingly be denied on this ground as well.

IV. PLAINTIFFS ATTEMPT TO EVADE THEIR EXPERTS' UNRELIABLE ANALYSIS OF STRENGTH OF ASSOCIATION BY MAKING BASELESS ALLEGATIONS OF CHERRY-PICKING.

Plaintiffs argue that defendants' experts' opinions regarding strength of association are not reliable because: (1) defendants' experts "disingenuously cherry-pick[ed] 'sound bites' from the PSC's experts";[156] and (2) strength is a

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association reported in the talc literature is weak, inconsistent and potentially spurious to begin with, as set forth herein and in defendants' General Causation Brief. Indeed, legal commentators and a number of courts have recognized that application of the Bradford Hill criteria should not proceed unless studies show an association that is not attributable to bias, chance or confounding. *See, e.g.*, Epidemiology Reference Manual at 598-99 ("In assessing causation, researchers first look for alternative explanations for the association, such as bias or confounding factors. . . . Once this process is completed, researchers consider how guidelines for inferring causation from an association apply to the available evidence. We emphasize that these [Bradford Hill] guidelines are employed ***only after a study finds an association*** to determine whether that association reflects a true causal relationship.") (emphasis added); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 916 (D.S.C. 2016) ("In assessing causation, epidemiologists 'first look for alternative explanations for the associations, such as bias or confounding factors,' and then apply the Bradford Hill factors to determine whether an association reflects a truly causal relationship.") (citing Epidemiology Reference Manual at 598-600); *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 188 (S.D.N.Y. 2009) ("[T]he [Bradford Hill] factors are meant to be used to 'distinguish causal from non-causal associations that were already "perfectly clear-cut and beyond what we would care to attribute to the play of chance."'") (citation omitted).

156 (Pls.' Br. at 66.)

"qualitative" rather than "quantitative" assessment.[157] These arguments, too, are thinly veiled attempts to salvage plaintiffs' experts' own unreliable opinions, and should be rejected as meritless.

First, plaintiffs' accusation of cherry-picking is misplaced and self-defeating. Essentially, plaintiffs accuse defendants' experts of "cherry-picking" language from plaintiffs' experts' reports to make it seem like plaintiffs' experts have characterized the strength of the talc-ovarian cancer association as, for example, "high."[158] According to plaintiffs, their experts actually eschewed labels such as "strong," "moderate" or "weak" altogether. This is facially wrong.

- Dr. Carson: "[T]hese epidemiological studies support a ***strong*** association between the perineal use of talcum powder and ovarian cancer."[159]

- Dr. Siemiatycki: "Thus, the 28% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. . . . Such a ***high and significant*** meta-RR could not have occurred by chance."[160]

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157 (*Id.* at 67.)

158 (*Id.* at 68, 71-72.)

159 (Carson Rep. at 10 (emphasis added).)

160 (Siemiatycki Rep. at 63 (emphasis added).) Dr. Merlo's quotation of this sentence in his report is the only specific example of supposed "cherry-picking" plaintiffs identify. (*See* Pls.' Br. at 71-72.) In the quote plaintiffs reference, Dr. Merlo opined that Dr. Siemiatycki's "insistence that a 1.28 relative risk is 'high'" indicates a "results-driven approach to their causation analysis." (*See id.*; Merlo Rep. at 44.) As shown above, there was nothing taken out of context with respect to this statement. Moreover, plaintiffs identify no specific instances of alleged

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- Dr. Singh: "I place significant weight on the fact that studies demonstrate a ***strong*** association between talcum powder use and ovarian cancer and show consistency of the data."[161]

- Dr. Moorman: "Taken as a whole, the ***overwhelming statistical strength*** of these studies, whose results are replicated over decades across a wide variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference."[162]

- Dr. Smith-Bindman: "[A]ssessing *strength of association* when inferring causality requires examining underlying research and analytic methods, comparing the weight of evidence in the literature, and considering other contextual factors. The data supporting the causality of talcum powder products [sic] exposure for ovarian cancer is ***extremely strong***."[163]

These are direct quotes, not "cherry-pick[ed] 'sound bites.'"[164] And as defendants have explained, these conclusions are at odds with the published literature and even plaintiffs' experts' own admissions at their depositions, which

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cherry-picking by Drs. Ballman and Diette, claiming only that they made "similar . . . criticisms" and citing their reports "generally." (Pls.' Br. at 72 & n.156.)

161 (Singh Rep. at 63 (emphasis added); *see also id.* at 17 (asserting that the "strength of association . . . is significant").)

162 (Moorman Rep. at 29 (emphasis added).)

163 (Smith-Bindman Rep. at 37 (emphases added).)

164 (*See* Pls.' Br. at 66.)

overwhelmingly refer to the association as "weak," "modest," or the like.[165] Plaintiffs' unwillingness to even attempt to defend the language their experts used in their reports in the face of this lack of scientific support is extraordinarily telling.[166]

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[165] Wynder 1982 at 465 ("the term 'weak' refers to relative risks between 1.0 and 2.0"); Draft Screening Assessment at 21 ("small" association); FDA Denial Letter at 4 ("small positive associations"); Berge 2018 at 248 ("weak" association). (*See also* Dep. of Anne McTiernan, M.D., Ph.D. ("McTiernan Dep.") 101:5-17, Jan. 28, 2019 (attached as Ex. B2 to Tersigni Cert.) (testifying that the World Cancer Research Fund concluded that "[e]ven if there were an increased risk, scientists estimate it would be small"); Dep. of Arch I. Carson, M.D., Ph.D. ("Carson Dep.") 230:18-231:5, 232:13-233:23, Jan. 19, 2019 (attached as Ex. B5 to Tersigni Cert.) ("weak or modest"); Dep. of Sarah E. Kane, M.D. 256:24-257:4 (attached as Ex. B45 to Tersigni Cert.) (similar); Singh Dep. 140:19-25 (similar); Clarke-Pearson Dep. 130:10-15 (failing to identify any peer-reviewed literature on talc and ovarian cancer that states 1.3 is a strong association); Moorman Dep. 251:9-13 (same); Singh Dep. 140:19-141:20 (same); Dep. of Ellen Blair Smith, M.D. ("Smith Dep.") 289:19-290:3, Jan. 9, 2019 (attached as Ex. B11 to Tersigni Cert.) (same).) Plaintiffs argue that the National Cancer Institute ("NCI") characterized a 1.2-1.8 association (for different variables) as "'moderate,'" but this is wrong. (Pls.' Br. at 68.) The NCI used the term "modest," not "moderate" in the discussion plaintiffs reference. 2019 NCI PDQ at 3 ("Magnitude of Effect: Modest with observed RRs of 1.20 to 1.8."). Regardless, plaintiffs ignore the NCI's conclusion that "[t]he weight of evidence ***does not support an association*** between perineal talc exposure and an increased risk of ovarian cancer," based in part on its observation that "[r]esults from case-control and cohort studies are inconsistent." *Id.* (emphasis added).

[166] Equally telling is the fact that plaintiffs chose to address strength of association last in their brief, after spending the bulk of it on consistency and attempting to downplay the importance of the dose-response and biological-plausibility factors. Strength of association is generally considered first in a Bradford Hill analysis, in part because, absent a sufficiently clear association, "there is no charter to undertake a Bradford Hill analysis at all." *In re Mirena*, 341 *(cont'd)*

Second, plaintiffs' contention that experts should address strength of association as a "qualitative" rather than "quantitative" issue[167] would effectively write the strength consideration out of Bradford Hill. There can be no question that Hill intended strength to be a quantitative factor. After all, in describing what he means by strength, Hill specifies a "200 times" increase in scrotal cancer among chimney sweeps and a "nine to ten times" increase in lung cancer among smokers.[168] Moreover, the Reference Manual expressly states that "[r]elative risk measures the strength of the association," and that, the "higher the relative risk, the greater the likelihood that the relationship is causal,"[169] similarly indicating a numerical focus. Consistent with this definition, courts have excluded experts who purport to reach causation opinions where, for example, "the strength of the

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F. Supp. 3d at 255, 258 (describing strength as a "threshold factor"); *see also* Hill 1965 at 295 ("First upon my list I would put the strength of association."); Epidemiology Reference Manual at 602 (second); *Zoloft III*, 858 F.3d at 795 (first). Strength also helps frame the broader Bradford Hill inquiry. As the Reference Manual explains, "[a]lthough lower relative risks can reflect causality, the epidemiologist will scrutinize such associations more closely because there is a greater chance that they are the result of uncontrolled confounding or biases." Reference Manual at 602. In other words, a scientist examining a weak association will demand more from the other Bradford Hill considerations than she or he might when considering a stronger association.

167 (Pls.' Br. at 68-71.)

168 Hill 1965 at 295.

169 Epidemiology Reference Manual at 602.

associations between exposure to Zoloft and various birth defects at issue is weak, often not greater than one would expect by chance alone." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 463 (E.D. Pa. 2014); *see also Carl*, 2016 WL 4580145, at *18 (observing that the talc studies showed a "uniformly weak . . . association" of approximately 1.3). Indeed, illustrating that the objective magnitude of an association is an important consideration, many courts recognize that "the threshold for concluding that an agent was *more likely than not* the cause of an individual's disease is a relative risk greater than 2.0." *See, e.g.*, *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D.N.J. 2002) (citation omitted), *aff'd*, 68 F. App'x 356 (3d Cir. 2003).

Plaintiffs' lone citation (once again) comes from Dr. Rothman, but even he cannot help them. After all, Dr. Rothman wrote only that "'a strong association is neither necessary nor sufficient for causality,'" while "'weakness is neither necessary nor sufficient for absence of causality.'"[170] In other words, Dr. Rothman was making the point that strength is just one of the Bradford Hill criteria, a principle with which all of defendants' experts agree. Of course, this does not mean that strength means something different from what Bradford Hill envisioned and that the numerical magnitude of an association should be ignored; to the

[170] (Pls.' Br. at 67 (quoting Rothman 2008 at 67).)

contrary, in commenting on how "strong" and "weak" associations should be treated, Dr. Rothman necessarily contemplates some assessment of effect magnitude.

Finally, plaintiffs' argument that strength of association should be assessed in comparison to "other exposures that are also causal" like second-hand smoke[171] makes no sense because those exposures were found to be causal ***despite*** a lack of strength, in large part because the other Bradford Hill considerations were more convincingly met, as explained in defendants' own General Causation Brief.[172] For this reason, plaintiffs' attempt to use second-hand smoke to their advantage backfires. In arguing that their experts took a supposedly "nuanced and scientific approach to the strength of association prong," plaintiffs quote their expert Dr. Moorman's comparison of the talc-ovarian cancer association to that between second-hand smoke and lung cancer.[173] But the study on which Moorman relied specifically noted that: (1) there were nearly identical results between cohort studies and case-control studies (i.e., consistency) and (2) there was a clear dose-

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171 (*Id.* at 68.)

172 (*See* Defs.' General Causation Br. at 43-46.)

173 (*Id.* at 68-70.)

response relationship.[174] As explained by defendants' experts and in defendants' briefing, neither is the case here.

In short, the existence of a causal relationship between second-hand smoke and lung cancer does not show that strength actually means weakness; rather, it shows that in certain circumstances, the strength criterion is not dispositive. That analogy offers no help to plaintiffs here, since there are no other criteria whose satisfaction overcomes the lack of strength in the epidemiology.

For all of these reasons, plaintiffs' arguments about defendants' experts' supposed cherry-picking are demonstrably false and only serve to highlight the methodological flaws of plaintiffs' own experts' analyses.

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[174] *See* Taylor et al., *Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent*, 36 Int'l J. Epidemiol. 1048, 1051 tbl. 4, 1052 (attached as Ex. A138 to Tersigni Cert.) (reporting statistically significant relative risks of 1.22 for seven cohort studies on second-hand smoke, 1.18 for 25 population-based case-control studies and 1.33 for 23 non-population-based case-control studies; further reporting that 20 of 36 studies reporting dose-response data showed a statistically significant trend) (cited in Moorman Rep. at 13). (*See also* General Causation Br. at 43-46 (explaining in more detail why plaintiffs' experts' comparison of the talc-ovarian cancer association to other diseases was not reliable).)

V. PLAINTIFFS' HALF-HEARTED ATTACKS ON DEFENDANTS' EXPERTS' QUALIFICATIONS ARE FRIVOLOUS.

Finally, plaintiffs criticize defendants' epidemiology experts' qualifications, although they apparently do not seek to exclude them on this ground.[175] This is an implicit concession that plaintiffs' qualifications arguments are frivolous.

As set forth supra, defendants' experts are amply qualified to evaluate epidemiological evidence, opine regarding general causation and criticize plaintiffs' experts' general causation opinions based on their significant background, training and experience in epidemiology. To take but one example, plaintiffs' complaint that Dr. Ballman is a biostatistician rather than an epidemiologist is laughable, given that Weil Cornell considered her sufficiently credentialed in epidemiology to appoint her as the "Chief of the Division of Biostatistics and Epidemiology at Weill Cornell Medicine."

Moreover, certain of plaintiffs' criticisms – i.e., that defendants' experts have not published their opinions and that they began studying whether talc use causes ovarian cancer in conjunction with being retained as experts[176] – apply equally to their own experts.[177] And while plaintiffs boast that their experts have

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175 (Pls.' Br. at 4-6.)

176 (*Id.*)

177 (*See, e.g.*, Clarke-Pearson Dep. 25:3-7 (stating that he formed his opinion that talcum powder causes ovarian cancer "sometime after [he was] contacted and

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"collectively published and spoken on topics related to the general causation questions in this MDL[,] including to Congress" and IARC,[178] they neglect to mention that when their experts Drs. Moorman and Siemiatycki published on talc use and ovarian cancer, they contradicted the causation opinions they now offer as litigation experts, as discussed in more detail in defendants' General Causation Brief.

CONCLUSION

For the reasons set forth above, the Court should deny plaintiffs' motion to exclude the opinions of defendants' experts Drs. Karla Ballman, Gregory Diette and Christian Merlo.

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retained in this matter"); Smith Dep. 83:9-13 (same); Dep. of Rebecca Smith-Bindman, M.D. 47:15-25, Feb. 7, 2019 (attached as Ex. B40 to Tersigni Cert.) (stating that prior to agreeing to retention, she "did not know this field in any great depth"); Singh Dep. 39:3-19; Carson Dep. 38:17-22 (both similar).) (*See also* Omnibus *Daubert* Opposition Brief at 5-8; Defs.' Mem. of Law in Supp. of Conditional Mot. to Exclude Certain Pls.' Experts' Ops. for Lack of Qualifications at 3-4, May 7, 2019 (ECF No. 9736-6).)

[178] (Pls.' Br. at 4.)

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Respectfully submitted,

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